REMARKS

I. Preliminary Remarks

Applicants thank Examiner Ronald Schwadron, Ph.D. for the courtesy of the interview kindly granted on November 18, 2004 to Applicants' attorneys Li-Hsien-Rin-Laures, Sharon Sintich and Rosemary Sweeney. During the interview, Applicants discussed the new claims presented herein, the outstanding restriction/election requirement, certain art that was previously cited by the Examiner during prosecution of the present application, and Applicants' evidence for non-obviousness. Although agreement with respect to the claims was not reached, the Examiner agreed to consider Applicants' new claims and evidence.

II. Prosecution History

A final office action was mailed for the present application on March 26, 2003, in which the Examiner rejected claims directed to a DNA segment encoding the extracellular domain of an insoluble human TNF receptor polypeptide having an apparent molecular weight of about (a) 55 kilodaltons or (b) 75 kilodaltons on a non-reducing SDS-polyacrylamide gel, functionally attached to an Fc portion and hinge region of an IgG heavy chain polypeptide (see claim 66 of Amendment dated January 14, 2003). In response to the final action, Applicants filed a Response to Final Office Action under Rules 116 and 129(a) on June 17, 2003. This response included an amendment that further amended the pending claims and added new claims directed to a method of making a recombinant DNA encoding a chimeric polypeptide, chimeric proteins encoded by the recombinant DNA and methods of making the chimeric proteins.

In view of the filing under 37 C.F.R. § 1.129(a) with the requisite fee, finality of the previous office action was withdrawn and the amendment was entered. In response to the amendment, the Examiner issued a restriction requirement stating that newly submitted claims 100-104 and 110-124 were directed to an independent or distinct invention from the invention originally claimed. The Examiner stated that Applicants had constructively elected DNA molecules and required Applicants to elect a species of human immunoglobulin (IgG, IgA, IgM or IgE) and if appropriate elect a species of IgG (IgG1 or IgG3). The Examiner did not require election of a species of TNF receptor (55 or 75 kD) at this time. In response, Applicants elected IgG1 (see page 2 of the Response dated March 22, 2004).

An Official Communication was subsequently mailed on June 9, 2004, which indicated the reply to the Restriction Requirement was not fully responsive because Applicants did not include an identification of the elected species and a listing of all claims readable thereon.

III. Election

During the interview, Applicants requested election of different Invention III (protein claims) and discussed the new claims presented herein with the Examiner, of which claims 125-149, 151, 153 and 154 correspond to Invention III. The Examiner did not make a final determination but agreed to consider Applicants' request. The Examiner also clarified that to be responsive to the prior restriction/election requirement, Applicants should elect an IgG isotype and state which of the new claims correspond to the elected isotype.

Within Invention III (protein claims), Applicants also hereby elect the species IgG1. All claims 125-154 read on species IgG1. If separate consideration of non-elected species IgG3 is deemed necessary, Applicants request consideration of the IgG3 species upon allowability of the generic claims. See MPEP §809.02(c).

The claims presented herein are directed to recombinant fusion proteins comprising a soluble fragment of a TNF receptor protein, having a molecular weight of about 75 kD, fused to all of the domains of the constant region of a human immunoglobulin heavy chain other than the first domain of said constant region.

Claims 150 and 152, which were presented during the interview, are directed to methods of making a recombinant protein of the invention. These claims are encompassed by Invention IV according to the Restriction Requirement. If the Examiner withdraws these claims as being directed to an independent and distinct invention, rejoinder may be available. Applicants request that method claims 150 and 152 be rejoined if the protein claims are found to be novel and non-obvious. See 1184 OG 86 (1996).

IV. Basis and Support for New Claims

During the interview, Applicants explained that the language of new claim 125 corresponds to the language of issued claim 1 of U.S. Patent No. 5,610,279. Applicants discussed one notable difference in the language of claim 125 which recites "human TNF receptor." Applicants stated that addition of the term "human" addressed the Examiner's

previous concern that the claims could read on thousands of mammalian species. (See Office Action of July 15, 2002, page 3.)

The new claims are supported by the specification throughout, *e.g.*, at page 11, lines 1-10, and do not add new matter to the application. Specific support for the newly added language in the claims is described in the following paragraphs.

Claims 127-129, 134-137, and 141-144 recite fragments of the p75 TNF receptor that are specifically identified as the peptides taught in the specification, *e.g.*, at page 7, line 34 (peptide IIB, VFCT), page 8, lines 5-6 (peptide IID, LPAEVAFXPYAPEPGSTC) and page 8, line 8 (peptide IIF, LCAP).

Claim 133 is directed to a protein encoded by a nucleic acid subsequence that hybridizes to a nucleic acid sequence of SEQ ID NO: 3. Nucleic acid sequences that hybridize with the nucleic acid sequence of Figure 4 (SEQ ID NO: 3) are supported throughout the specification, particularly at page 9, lines 31-32, page 10, lines 11-26 and in Example 8 (pages 34-35).

Claims 134 and 144 are directed to recombinant proteins encoded by a nucleic acid subsequence obtainable by a method comprising a step of hybridizing an oligonucleotide probe to a cDNA library made from HL60 cell extracts. Methods of obtaining nucleic acid sequences from a HL60 cDNA library using probes derived from peptide sequences are taught, *e.g.*, at page 14, lines 7-36, page 6, lines 10-16 and in Example 8 (page 35, lines 23-36).

Support for the language in claims 125, 133 and 141 that the recombinant protein exhibits specific TNF binding activity is found throughout the specification in the concept that the invention is directed to TNF binding proteins, including in Example 1 (page 21, lines 6-22) which notes that the desired TNF binding proteins have specific TNF binding activity.

Claims 148 and 149 recite the vectors pCD4Hγ1 and pCD4Hγ3. These vectors are supported in the specification, most particularly, at page 17, lines 25-31.

Claims 150-153 are directed to methods of making a recombinant protein comprising the steps of culturing a host cell which expresses the protein and isolating the

protein from the host cell or culture supernatant. These claims are supported throughout the specification, especially at page 6, lines 22-29 and page 12, lines 4-8.

Claim 154 is directed to compositions comprising pharmaceutically acceptable carrier material. This claim is supported, *e.g.*, at page 12, lines 10-15.

Applicants have also added a sequence listing in compliance with sequence listing requirements. The table below shows how the sequences of the sequence listing correspond to the sequences in the figures and the peptides IIA-IIH of p75 TNF receptor in the specification. Applicants note that SEQ ID NOS: 3 and 4 are identical to Figure 4 except they also include the sequence correction noted at page 35, lines 32-36 of Example 8 (amino acid at position 3 is Thr instead of Ser as it is encoded by "ACC" not "TCC").

SEQ ID NO:	As Reference in the Specification	Page and Line Number
1	p55 kD TNF Receptor cDNA sequence	Figure 1; page 4, lines 16-21
2	p55 kD TNF Receptor deduced amino acid sequence	Figure 1; page 4, lines 16-21
3	p75 kD TNF Receptor cDNA sequence	Figure 4; page 4, lines 35-36
4	p75 kD TNF Receptor deduced amino acid sequence	Figure 4; page 4, lines 35-36
7	Peptide IIA	page 7, lines 32-33
8	Peptide IIB	page 7, line 34
9	Peptide IIC	page 8, lines 3-4
10	Peptide IID	page 8, lines 5-6
11	Peptide IIE	page 8, line 7
12	Peptide IIF	page 8, line 8
13	Peptide IIG	page 8, line 9
14	Peptide IIH	page 8, line 10

V. Declaration of Dr. Werner Lesslauer

During the interview, Applicants also discussed U.S. Patent No. 5,428,130 (referred to herein as "Capon") with the Examiner. Applicants pointed out that Capon discloses a large variety of different types of Ig fusions and states that the specific site of fusion is not important. Capon indicates that any site of fusion may be used to create the immunoglobulin fusion proteins (See column 10, lines 30-35). Capon also states that a variety of configurations (*e.g.*, monomeric, dimeric, tetrameric, homomultimeric, or

heteromultimeric) are possible (col. 10, lines 36-38). The subsequent pages of Capon depict the wide variety of possible fusion proteins.

It was the Examiner's position during the interview that Capon, if combined with other art teaching the TNF receptor sequence, would render obvious claims to TNF receptor-Ig fusion proteins. In response, Applicants present evidence of nonobviousness with respect to IgG1 and IgG3 fusions that would overcome such a rejection.

Attached is a declaration under 37 C.F.R. § 1.132 of Dr. Werner Lesslauer (referred to herein as the "Declaration") which provides experimental evidence demonstrating unexpected results with an IgG3 fusion protein of the claims presented herein. The Declaration provides experimental data obtained using a recombinant fusion protein comprising the extracellular domain of the 75 kD TNF receptor (also known as TNFR-II) fused to the hinge region of IgG3 (denoted as "p75sTNFR/IgG" in the Declaration). See paragraph 4 of the Declaration. As the spatial geometry of the TNF receptor binding site was not known, it was possible that p75sTNFR/IgG would not even exhibit TNF binding activity (see page 2, Exhibit B.) Dr. Lesslauer states: "Surprisingly, however, the fusion construct obtained even had an excellent binding activity. In addition, an unexpectedly higher kinetic stability and a surprisingly improved inhibition of the effect of TNFα in biological cell culture tests were discovered as well." (Page 2 of Exhibit B of the Declaration)

Experiment I in the Declaration is a binding study that measured dissociation of the test TNF binding protein from radiolabeled TNFα in the presence of unlabeled TNFα. Dissociation of p75sTNFR/IgG fusion was compared to dissociation of p75sTNFR fragment. As shown in the figure, at the six-minute time point, essentially all of the TNFα had dissociated from p75sTNFR, while only about half of the TNFα had dissociated from p75sTNFR/IgG, which indicates p75sTNFR/IgG has a higher kinetic stability than sTNFR.

Experiment II of the Declaration investigates the effect of p75sTNFR/IgG on TNF-induced proliferation of mononuclear cells as measured by incorporation of radiolabeled thymidine. As demonstrated in the table, p75sTNFR/IgG inhibited 86% of TNF-induced proliferation while p75sTNFR inhibited 68% of TNF-induced proliferation. This data demonstrated that p75sTNFR/IgG was more effective in neutralizing TNF biological activity. Note that because equal weight amounts of p75sTNFR and p75sTNFR/IgG (which is twice as heavy as p75sTNFR) were added to the cell culture, on a molar basis only half as much

p75TNFR/IgG was used in Experiment II. Thus, half as much of the IgG3 fusion protein provided a signficantly greater neutralization of TNF biological activity.

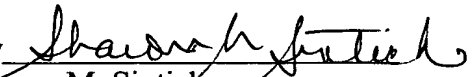
Further, published data in Mohler et al., *J. Immuno*l. 151:1548-1561, 1993 (denoted as "Mohler *et al.*" and attached herewith) provides experimental evidence demonstrating unexpected results with an IgG1 fusion protein of the claims presented herein. In the studies described in Mohler *et al.*, the extracellular portion of p80 TNFR (also known as TNFR-II) fused to the Fc portion of human IgG1 (see page 1554, col. 2 bottom) lacking the CH1 domain (see Fig. 1 at page 1550) to make an immunoglobulin fusion protein called sTNFR:Fc. As depicted in Figure 2 of Mohler *et al.*, the sTNFR:Fc had about 50 fold higher binding affinity for TNF than the sTNFR (page 1550, col. 2 and Fig. 2A). In addition, the sTNFR:Fc was about 1000 fold more effective in neutralizing TNF-induced cytotoxicity in L929 cells (page 1551, col. 1 and Fig. 2B). Therefore, in addition to the unexpectedly increased binding affinity of the fusion protein as compared to the extracellular domain alone (an approximately fifty fold increase), the sTNFR:Fc fusion protein also displayed increased biological activity in an *in vitro*, cell-based assay that was unexpected in magnitude (about 1000 fold) on the basis of the already unexpectedly increased binding affinity.

CONCLUSION

In view of the above remarks, Applicants believe claims 125-154 are in condition for allowance. If further discussion or amendments would expedite allowance of the claims, the Examiner is asked to contact the undersigned at the number below.

Dated: December 9, 2004

Respectfully submitted,

By 

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